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Some Chemical Reactions of BZ (U)

by
Brennie E. Hackley, Jr.
Chappelle C. Cochrane
Ethel B. Hackley

May 1964

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U. S. Army Edgewood Arsenal
CHEMICAL RESEARCH AND DEVELOPMENT LABORATORIES
Edgewood Arsenal, Maryland

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(U) **FOREWORD**

This work was conducted under Task 4C08-03-016-14, Biochemical Action of Chemical Agents (U). The experimental data are contained in notebooks MN-1452, MN-1465, MN-1440, MN-1400, and MN-1587. The work was started in March 1961 and completed in April 1962.

Acknowledgments

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(C) DIGEST

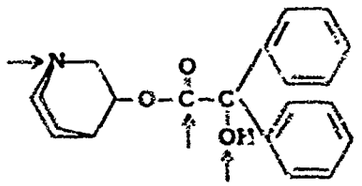
A fundamental study of the chemistry of BZ was conducted to assist in problems that may arise in detection, decontamination, biochemical mechanism of action, and metabolism. BZ reacts with (a) substituted phenyl isocyanates to yield 2,4-oxazolidinediones, (b) nitriles to produce amides (Ritter reaction), and (c) alkyl halides to give quaternary ammonium salts. Analysis of BZ can be accomplished by quaternization in acetonitrile, separation of reactants, and assaying spectrally.

(S) SOME CHEMICAL REACTIONS OF BZ (U)

(S) INTRODUCTION

(U) BZ is a compound that has been type classified as an incapacitating chemical agent. To assist in the evaluation of the biological properties of the agent, and problems of manufacture, storage stability, detection, decontamination, biochemical mechanism of action, and metabolism, a fundamental study of the chemistry of BZ has been made.

(S) In the chemical structure of BZ there are three primary reactive sites: (a) the tertiary alcohol (b) the ester linkage, and (c) the quinuclidinyl



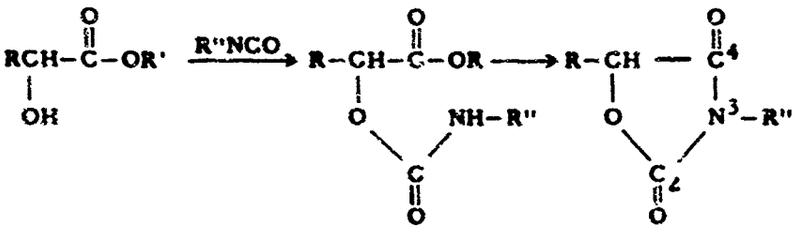
nitrogen atom. A survey of the literature (open and classified) on benzilate esters containing a tertiary nitrogen in the β-position of the alcohol moiety[1, 2, 3, 4] shows that most attention has been directed to reactions at the tertiary nitrogen, i.e., quaternization and salt formation, while little has been done on the direct reactions of the hydroxyl function. A considerable effort has been expended in these Laboratories on the hydrolytic cleavage of BZ. The purpose of this research was to study reactions of the tertiary hydroxyl group as well as reactions specific for benzilate esters that involve a bifunctional or two centered attack on the alcohol and ester linkage. In addition, some previously unreported quaternary salts were prepared as models to assist in the analysis and identification of BZ and its metabolic products.

II (S) PROCEDURES AND RESULTS.

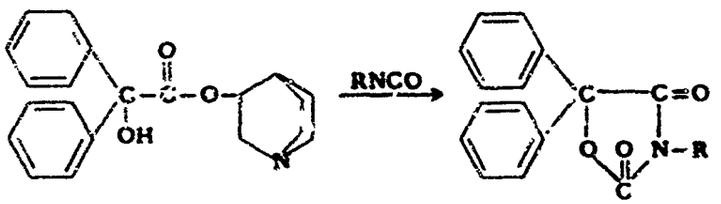
A. (S) 2,4-Oxazolidinediones.

(S) One of the classic modes of formation of 2,4-oxazolidinediones results from the reaction of an α-hydroxy ester and an isocyanate to form the

corresponding urethane, which is subsequently cyclized by heat or alkaline catalysts to the requisite oxazolidinedione.[5]



(S) In the special case of benzilate esters, the oxazolidinediones are formed spontaneously, even at low temperatures, on reaction with an isocyanate.[6] This type of two-centered attack would be specific for benzilate esters such as BZ. By judicious selection of the isocyanate, the N-substituted-5, 5-diphenyl oxazolidinedione (obtained as a single product) could possibly be analyzed by fluorescent, colorimetric, infrared, or other physical



analytical means that would provide an unequivocal assay of the benzilate to the total exclusion of other metabolic fragments.

1. (U) General Procedure for the Preparation of Oxazolidinediones From BZ.

A mixture of 1 gm (0.003 mole) of BZ, 0.003 mole of isocyanate, and 10 ml of dry benzene was refluxed for 1 hr. The cooled benzene solution was filtered and the filtrate evaporated to dryness under vacuum. The residue crystallized from isopropyl alcohol afforded the oxazolidinedione

2 (U) Results.

The oxazolidinediones prepared are listed in table I They all exhibit characteristic infrared absorptions in the regions of 5.5μ (urethane) and 5.7μ (amide).

B (S) Ritter Reaction Products

(S) Ritter et al[7] reported the reaction of nitriles with alkenes or tertiary alcohols to form N t-alkyl amides The presence of a tertiary alcohol group in BZ suggested the possible application of this reaction to BZ.

1 (U) General Procedure for the Ritter Reaction.

A solution of 1 gm (0.003 mole) of BZ and 0.004 mole of nitrile in 10 ml of glacial acetic acid was chilled in an ice bath and 15 ml of concentrated sulfuric acid added dropwise at a rate such that the temperature was maintained between 5° to 10°C. The reaction mixtvre was stirred cold for 1 hr and at room temperature for 2 hr The solution was poured onto crushed ice and neutralized with saturated potassium carbonate solution, then extracted with chloroform. The extract was dried over anhydrous potassium carbonate or sodium sulfate and the solvent removed. The residue was crystallized from benzene or benzene petroleum ether (bp 30° to 60°C) to yield the desired products

2 (S) Results

Table 2 lists the Ritter products prepared They are colorless, crystalline solids with definite melting points and show no unusual characteristic absorptions upon infrared analysis

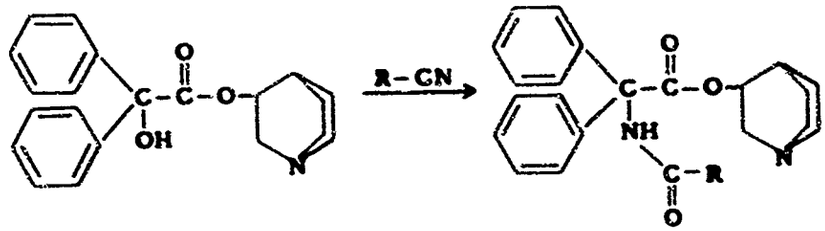


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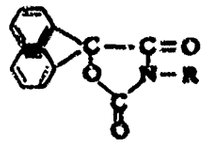
TABLE I

2,4-OXAZOLIDINEDIONES



R-	Melting point	Formula	Yield	Carbon		Hydrogen	
				Calculated	Found	Calculated	Found
	°C		%	%			
	141-143	$C_{21}H_{15}O_3N$	87	76.6	75 9	4 6	4.6
	131-132	$C_{21}H_{14}O_3NBr$	81	61.8	61 4	3 4	3.4
	117-118	$C_{22}H_{17}O_3N$	87.5	76.9	76.9	5.0	5.0
	129	$C_{22}H_{17}O_4N$	09	73.5	73.1	4.8	4.4
	148-149	$C_{21}H_{14}O_5N_2$	90	67.4	67.2	3 3	3 8
	155-156	$C_{23}H_{20}O_3N_2$	80	74.2	72.9	5 4	5 3
	148-150	$C_{25}H_{17}O_3N$	61	79.1	77.6	4.5	5 4
	153-154	$C_{27}H_{19}O_3N_3$	72	74.8	74.8	4 4	4.6
	136-138	$C_{27}H_{19}O_3N$	83	80.0	80.4	4.7	5.2

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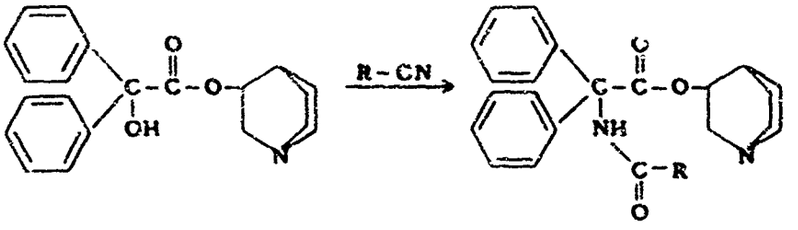

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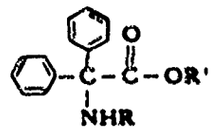
TABLE 2

RITTER REACTION PRODUCTS



R-	R'	Melting point °C	Yield %	Formula	Carbon Calculated %	Carbon Found %	Hydrogen Calculated %	Hydrogen Found %
$CH_3-C(=O)-$	Quinuclidine	179-180	76	$C_{23}H_{26}O_3N_2$	73.0	73 8	6 9	7 1
$CH_3CH_2-C(=O)-$	Quinuclidine	214-215	69	$C_{24}H_{28}O_3N_2$	73 44	73 6	7 2	6 9
$C_6H_5-C(=O)-$	Quinuclidine	96-99	50	$C_{28}H_{28}O_3N_2$	76 3	73 6*	6 4	5 9*
$NH_2-C(=O)-CH_2-C(=O)-$	Quinuclidine	112-113	66.5	$C_{24}H_{27}O_4N_3$	71	70 9	6 7	6 7
$CH_3-C(=O)-$	Methyl	169-172	95		72 1	71.8	5 9	5 1

* The carbon and hydrogen analyses of this reaction product deviate from theo[illegible] no attempt was made to further purify the substance.

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C. (S) Quaternary Ammonium Compounds.

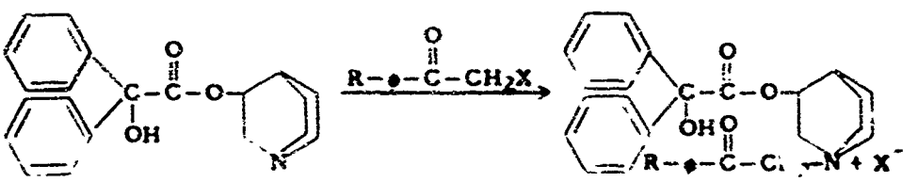
(C) When a tertiary base is quaternized with an alkylhalide, the differences in solubility of the salt-like product and the starting materials should be sufficient to allow spectral determination of the base. Several substituted phenacyl bromide quaternaries of BZ were prepared

1 (C) General Procedure for Preparation of Quaternary Salts.

A mixture of 1 gm (0.003 mole) of BZ, 0.004 mole of the phenacyl bromide, and 25 ml of chloroform was allowed to stand at room temperature for 18 hr. The solvent was removed under vacuum and the residue was crystallized from ethanol-ether, acetonitrile-ether or ethanol-1,2 dimethoxyethane.

2. (S) Results.

These products, typical high-melting crystalline solids, are listed in table 3



D. (C) BZ Acetate.

As part of this overall program, the authors were interested in preparing the acylated derivatives of BZ. In this connection attempts were made to acetylate BZ with acetic anhydride and with acetyl chloride in pyridine to no avail. The infrared spectrum of BZ indicates strong intramolecular, or intermolecular hydrogen bonding, which is absent in its salts. The nonreactivity observed with the usual acetylating reagents may be due to this bonding as well as to steric factors. Thus, treatment of the p-toluenesulfonic acid salt of BZ with isopropenyl acetate afforded the acetate quite smoothly.

(C) TABLE 3

PHENACYL BROMIDE QUATERNARY SALTS OF BZ (C)

Alkyl halide	Melting point	Yield	Carbon		Hydrogen	
			Calculated	Found	Calculated	Found
	°C	%	%			
p-Phenylphenacyl bromide	214-215	92	68.68	68.9	5.4	5.7
p-Nitrophenacyl bromide	190-191	99	59.9	58.3	5.1	5.3
p-Bromophenacyl bromide	170-175	90	56.6	56.6	4.8	4.8
β-Naphthacyl bromide	220-224	93	67.7	67.5	5.5	5.4

A mixture of 2 gm (0.0039 mole) of the p-toluenesulfonic acid salt of BZ, mp 180° to 182°C, 20 ml of isopropenyl acetate and a few crystals of p-toluenesulfonic acid was refluxed; acetone was distilled off slowly over a period of 5 hr. The mixture was homogeneous at this time. The excess isopropenyl acetate was removed under vacuum and the residue made alkaline with cold saturated potassium carbonate solution. This was extracted with chloroform, dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The residue was refluxed with diethyl ether, filtered, and cooled to room temperature, it yielded 0.68 gm, 44.5%, of the acetate, mp 121° to 123°C.

Calculated: C, 72.8; H, 6.64
Found. C, 72.7 H, 6.7

E. (C) Spectrophotometric Determination of Small Quantities of BZ

p-Bromophenacyl bromide reacts readily with BZ in acetonitrile forming a quaternary salt. Since quaternary salts have relatively high solubility in water, one may separate the product from reactants and thus determine the amount of tertiary amine originally present. A plot of absorbancy versus concentration follows Beer's law. Detailed procedures for the determination of BZ in (a) acetonitrile, (b) water, and (c) in human whole blood follow.

Reagents: Recrystallized p-bromophenacyl bromide, spectrograde acetonitrile, chloroform, CP, 0.1 M tris(hydroxymethyl)aminomethane (tris) buffer (pH 8.5), cyclohexane, and BZ.

1 (C) Determination of BZ in Acetonitrile.

(C) To 0.1 ml of 10^{-2} M solution of p-bromophenacyl bromide in acetonitrile in a glass-stoppered bottle is added 1 to 40 µg of BZ dissolved in 1 ml of acetonitrile. The solution is mixed and heated in a 50°C water bath for 10 min. After cooling the solution to room temperature, 2 ml of 0.1 M KCl and 5 ml of cyclohexane are added and the mixture is mechanically shaken for 5 min. A portion of the aqueous phase is read spectrophotometrically at 265 mµ and the adherence to Beer's law demonstrated (table 4, figure 1).

(U) TABLE 4

DETERMINATION OF BZ IN ACETONITRILE

BZ	Absorbancy*
µg/ml	
0	0.066
2.6	0.205
5.2	0.328
7.8	0.456
10.4	0.597
13.0	0.738

* Average of five determinations

2. (C) Determination of BZ in Aqueous Solutions.

(C) To 2-ml aqueous solutions of BZ (5 to 40 µg) are added 0.2 ml of tris buffer (pH 8.5) and 3 ml of chloroform. The mixture is shaken mechanically for 5 min and the aqueous layer removed. An aliquot of the chloroform layer is air evaporated and the residue dissolved in 1 ml of acetonitrile. The analysis is then made in the manner reported above (E.1.) (table 5, figure 2).

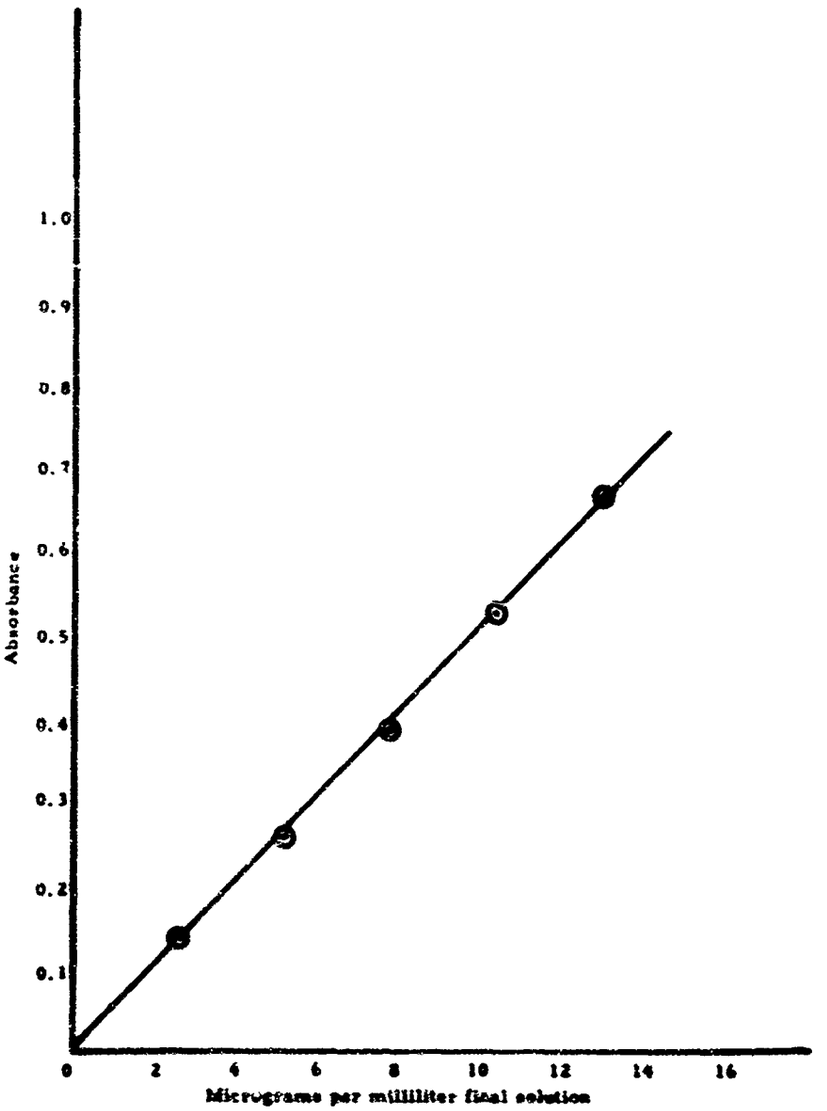


FIGURE 1

DETERMINATION OF BZ IN ACETONITRILE

(U) TABLE 5

DETERMINATION OF BZ IN AQUEOUS SOLUTIONS

BZ	Absorbancy*
ug/ml	
0.62	0 018
1.25	0.058
2.5	0.101
5.0	0.253
7.5	0.391
10.0	0.517
12 5	0 64[9]

* Average of five determinations.

3. (C) Determination of BZ in Human Whole Blood.

(C) To 1 ml of human whole blood is added a 1-ml aqueous solution of BZ. The mixture is diluted to 7 ml and thoroughly mixed. One milliliter of 50% $ZnSO_4$ is added, mixed, and followed by 1 ml of 0.3 N $Ba(OH)_2$. Chloroform (10 ml) is added and the mixture is shaken mechanically for 10 min. It is then transferred to a glass-stoppered centrifuge tube and spun at 2500 rpm for 10 min. A 4-ml aliquot of the chloroform layer is air evaporated and the analysis performed in acetonitrile as above (table 6, figure 3).

(U) TABLE 6

DETERMINATION OF BZ IN WHOLE BLOOD

BZ	Absorbancy*
ug/ml	
1 7	0 062
3.4	0 148
5.1	0 230
5.9	0.280
6.8	0.317
8 5	0.388
10.2	0.478

* Average of four determinations.

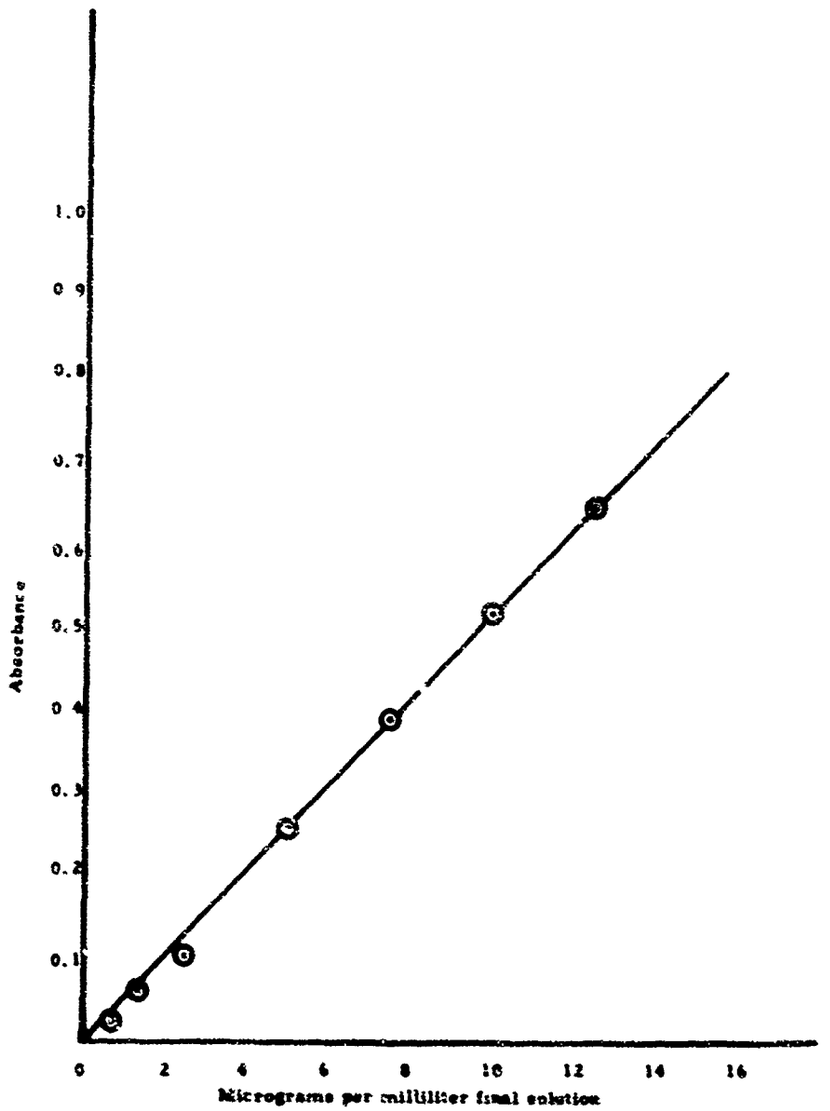


FIGURE 2

ANALYSIS OF BZ IN AQUEOUS SOLUTIONS

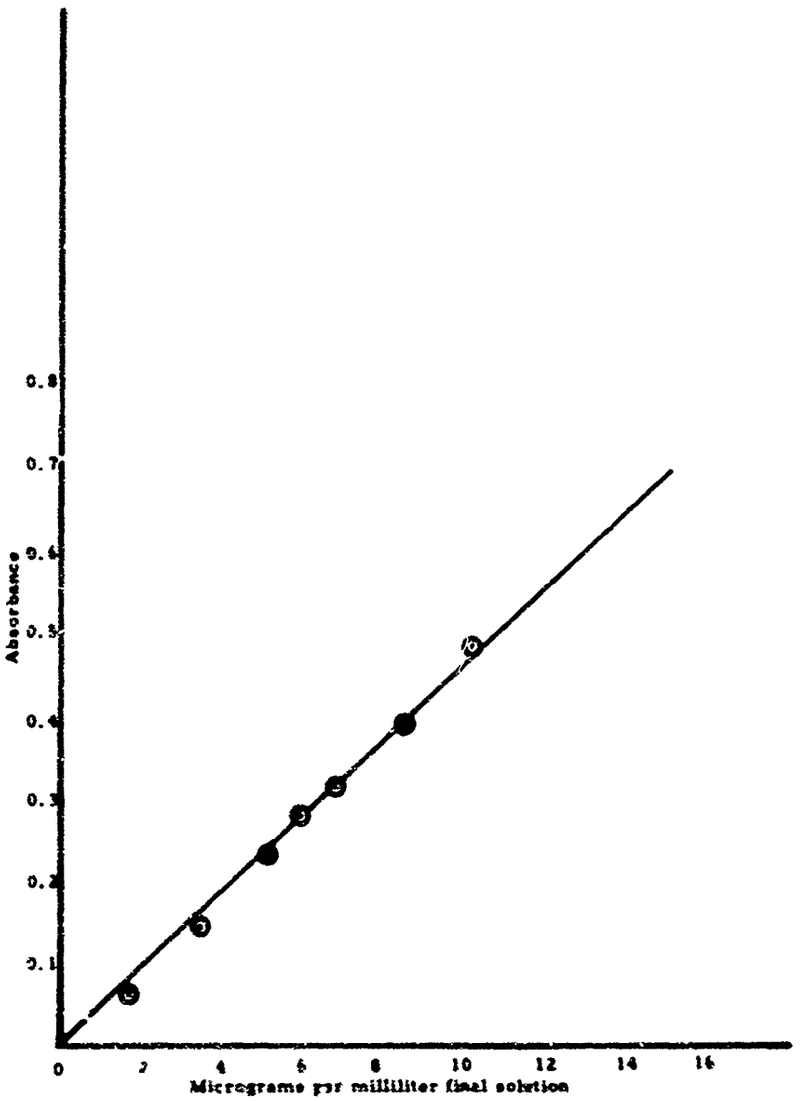


FIGURE 3

ANALYSIS OF BZ IN BLOOD

III. (C) CONCLUSIONS.

A fundamental study of the chemistry of BZ was conducted to assist in problems that may arise in detection, decontamination, biochemical mechanism of action, and metabolism. BZ reacts with (a) substituted phenyl isocyanates to yield 2,4-oxazolidinediones, (b) nitriles to produce amides (Ritter reaction), and (c) alkyl halides to give quaternary ammonium salts. Analysis of BZ can be accomplished by quaternization in acetonitrile, separation of reactants, and assaying spectrally.

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127 - 130	USA CDC Liaison Officer, Hq. U. S. Army Munitions Command, Dover, New Jersey - 07801
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ABSTRACT

1 Originating Activity

Physiology Division
U S Army Chemical Research
and Development Laboratories
Edgewood Arsenal, Maryland

2a Report Security Classification

SECRET

2b Group (for DDC use only)

3 Report Title SOME CHEMICAL REACTIONS OF BZ (U)

4 Descriptive Notes The work was started in March 1961 and completed in April 1962

5. Authors Hackley Brennie E Jr Cochrane, Chappelle C.
Hackley, Ethel B

6 Publication Date May 1964

7 Total No. of Pages 24

8 Originator s Report No

CRDLR 3213

9 Task 4C08-03 016 14

10. Other Report Nos.

11 Supplementary Notes
(for DDC use only)

12. Release Statements (for DDC use only)

13. Author's Key Terms - Unclassified Only

BZ	Mechanism of action
Chemical reactions	Amides
Detection	Ritter reaction
Decontamination	Alkyl halides
Biochemistry	Ammonium salts
Metabolism	Quaternization
Substituted compounds	Acetonitrile
Phenyl isocyanates	Spectrum
Chemical agents	2,4-oxazolidinediones
Nitriles	Biochemical action
Incapacitating agents	

14. DDC Descriptors (for DDC use only)

15 Identifiers - Unclassified Only

16. Body of Abstract

(C) The purpose of this work was to conduct a fundamental study of the chemistry of BZ, to assist in problems that may arise in detection, decontamination, biochemical mechanism of action, and metabolism. BZ reacts with (1) substituted phenyl isocyanates to yield, 2,4-oxazolidinediones, (2) nitriles to produce amides (Ritter reaction), and (3) alkyl halides to give quaternary ammonium salts. Analysis of BZ can be accomplished by quaternization in acetonitrile, separation of reactants, and assaying spectrally.

17. Indexing Annotation

Fundamental study of the chemistry of BZ to assist in the solution of problems of manufacture, storage, detection, decontamination, and biochemical mechanism of action.

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DEPARTMENT OF THE ARMY
US ARMY RESEARCH, DEVELOPMENT AND ENGINEERING COMMAND
EDGEWOOD CHEMICAL BIOLOGICAL CENTER
5183 BLACKHAWK ROAD
ABERDEEN PROVING GROUND, MD 21010-5424

REPLY TO
ATTENTION OF

AMSRD-ECB-TD

27 MAY 2009

MEMORANDUM FOR Army Declassification Activity, 8850 Richmond Highway, Suite 300, IMP Building, Alexandria, VA 22309

SUBJECT: Declassification Review

1. References:

a. Executive Order 12958, Classified National Security Information, dated 17 April 1995.

b. Executive Order 13292, Classified National Security Information, dated 25 March 2003.

c. AR 380-5, DA Information Security Program, dated 31 October 2000.

2. In accordance with the references listed above, the purpose of this memorandum is to provide the recommendation made by the Edgewood Chemical Biological Center (ECBC) Security Classification Review Board (SCRB), regarding declassification and downgrading of the below listed documents.

a. Isokinetic Sampling of H Aerosol, (ADA Case 08019), (as Produced by the Comings Candle), February 1946. Downgrade from Confidential to Unclassified/Unlimited.

b. Dugway Proving Ground Research and Development Weekly Report (Part A), Medical Research Laboratory Weekly Report (Part B), Dugway Proving Ground Mobile CWS Unit Weekly Report (Part C), (ADA Case 08024), February 1945. Distribution authorized to U.S. Government agencies and their contractors. Downgrade from SECRET to Unclassified/Unlimited.

c. Dugway Proving Ground Research and Development Weekly Report (Part A), Medical Research Laboratory Weekly Report (Part B), Dugway Proving Ground Mobile CWS Unit Weekly Report (Part C), (ADA Case 08023), January 1945. Downgrade from SECRET to Unclassified/Unlimited.

d. Counter-Insurgency and Air Power: Report of a Rand Ad Hoc Group, (ADA Case 07078), June 1962. Downgrade from SECRET to Unclassified/Unlimited.

e. The Role of Chemical and Biological Weapons in the Defense Strategy of the United States, (ADA Case 08002), December 1964. Retain at Confidential. 07-M-2834

07-M-2825, 07-M-2831,
07-M-2834 through 07-M-2838
07-M-2842

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SUBJECT: Declassification Review

f. Special Report: The Increment Flow Regulation Valve, (ADA Case 08020), 3 December 1945. Distribution authorized to US Government agencies only.

g. Interim Report: Development of Decontamination Solution Unit, 3-Gallon, E8R2, (ADA Case 08003), 15 February 1954. Retain at Confidential. 07-M-2836

h. Chemistry of BZ.I. Reaction of BZ with Iodine in Aqueous and Organic Solution, (ADA Case 08007), November 1962. Downgrade from Confidential to US Government Agencies and their contractors. 07-M-2837

i. Interim Report: Decontamination of Airplanes (F.Y. 53), (ADA Case 08006), 19 November 1953. Retain at Confidential.

j. Chemical Defense Experimental Establishment Portion, (ADA Case 08010), 4 December 1954. This document contains Foreign Government Information (British) and the decision should be deferred to them.

k. An Evaluation of the Relative Efficacy of Five Self-Injection Ampoules, (ADA Case 08011), December 1952. This document contains Foreign Government Information (British) and the decision should be deferred to them.

l. Infrared Spectra and Absorption Coefficients for GA, GB, GD, VM, VX, and the G analog (Reaction Product of VX and Conversion Filter), (ADA Case 08000), August 1966. Retain as US Government Agencies and their contractors. 07-M-2825

m. Estimate of Minimal Effective Dose of BZ by the Intramuscular Route in Man, (ADA Case 08004), November 1965. Downgrade from Confidential to Unclassified, US Government agencies and their contractors. 07-M-2831

n. Stability Testing of M138 BZ Bombs, (ADA Case 08008), August 1966. Downgrade from Confidential to Unclassified, US Government agencies and their contractors. 07-M-2835

o. Some Chemical Reactions of BZ, (ADA Case 08009), May 1964. Downgrade from Confidential to Unclassified/Unlimited. 07-M-2838

3. The point of contact is Mr. Jeremy Taylor at 410-436-6810 or jeremy.taylor2@us.army.mil.

for RICHARD W. DECKER, II
Technical Director